FROM GENES TO PERSONALIZED MEDICINES

Progress from the National Institute of General Medical Sciences

EVERYONE RESPONDS DIFFERENTLY TO MEDICINES. The dose of a drug that cures one person can be ineffective—or even toxic—in someone else. The reason? Genes (although a person's age, weight, lifestyle, and other medicines also play a role).

By understanding the genetic basis of drug responses, scientists hope to enable doctors to prescribe the drugs and doses best suited for each individual.

Scientists studying how genes affect responses to drugs are engaged in an active field of research known as pharmacogenetics or pharmacogenomics. (These terms are often used interchangeably, although to scientists they can have subtly different meanings.)

These researchers focus on variations in the molecules that interact with medicines moving through the body. Variations in these molecules are largely responsible for individual differences in drug responses.

THE ANTICIPATED BENEFITS OF PHARMACOGENETICS RESEARCH INCLUDE:

More Accurate Dosing

Instead of basing a starting dose on characteristics like weight and age, doctors may use a patient's genetic profile to predict how well his or her body will handle a medicine. Then, doctors could adjust the dose accordingly.

New, More Targeted Drugs

Pharmaceutical companies would be able to develop and market drugs for people with specific genetic profiles. Testing a drug only in those likely to benefit from it could streamline clinical trials and speed the process of getting a drug to market.

Improved Health Care

In the future, doctors may be able to prescribe *the right dose of the right medicine the first time for everyone.* This would mean that patients receive medicines that are safer and more effective for them, speeding recovery and reducing adverse drug reactions (estimated at 100,000 deaths and 2 million hospitalizations annually in the United States[1]). In this way, taking individual genetic profiles into account when developing and prescribing medicines would lead to better health care overall.

This echoes the vision of Health and Human Services Secretary Michael O. Leavitt, who states in his 500-Day Plan[2] that he foresees "a nation in which…medications are safer and more effective because they are chosen based on the patient's personal characteristics."

NIH NETWORK LEADS THE WAY

Scientists now have access to the sequence of all human genes, thanks to the Human Genome Project. Many prominent scientists predict that one of the first clinical applications of genomics will be testing patients for pharmacogenetic variants.[3]

To capitalize on this opportunity, the National Institute of General Medical Sciences (NIGMS), together with other components of the National Institutes of Health (NIH), established the NIH Pharmacogenetics Research Network in 2000. This network is a nationwide collaboration of researchers and doctors who study genes and medicines relevant to a wide range of diseases, including asthma, depression, cancer, and heart disease. They share their findings in a knowledge base available to all scientists (http://www.pharmgkb.org/). NIGMS also supports research on the ethical, legal, and social implications of the use of pharmacogenetic information.

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[1] JAMA. 1998 Apr 15;279(15):1200-5.
[2] http://www.hhs.gov/500DayPlan/500dayplan.html
[3] This type of testing examines how genes influence a person's response to medicines—it does not test for susceptibility to diseases.

NIGMS (http://www.nigms.nih.gov), a component of the National Institutes of Health in the U.S. Department of Health and Human Services, supports basic biomedical research that is the foundation for advances in disease diagnosis, treatment, and prevention.

In the network's first 5 years, its researchers made nearly 400 discoveries, including those described below.

Improving Breast Cancer Therapy
Individuals with a specific genetic variation in an enzyme called CYP2D6 do not respond well to tamoxifen, a common breast cancer drug. This finding may lead to greater use of genetic tests to identify which women are most likely to benefit from tamoxifen.

Tuning Blood Thinner Dosing
Every year in the United States, 2 million surgical and cardiac patients take warfarin (Coumadin®) to prevent blood clotting. Finding the correct dose for each person is notoriously difficult, and mistakes can be life-threatening. Researchers found that differences in a gene called VKORC1 influence how much warfarin is optimal for each person, a discovery that may enable faster and more precise dosing.

Optimizing Asthma Treatment
Researchers discovered that variations in some genes, including CRHR1 and ADRB2, affect the way people respond to asthma medicines (inhaled steroids and beta agonists). The team is now developing prototype tests for the gene variants to help doctors make treatment decisions.

In September 2005, NIGMS renewed the NIH Pharmacogenetics Research Network, promising a steady stream of advances during the next 5 years.

For more information on the network, go to http://www.nigms.nih.gov/Initiatives/PGRN/.

THE NIH PHARMACOGENETICS RESEARCH NETWORK GROUPS AND LEAD SCIENTISTS

Consortium on Breast Cancer Pharmacogenomics
David Flockhart, *Indiana University School of Medicine*

Functional Polymorphism Analysis in Drug Pathways
Howard McLeod, *Washington University in St. Louis*

Pharmacogenetics and Pharmacogenomics Knowledge Base
Russ Altman, *Stanford University School of Medicine*

Pharmacogenetics of Anticancer Agents
Mark Ratain, *University of Chicago*
Mary Relling, *St. Jude Children's Research Hospital*

Pharmacogenetics of Asthma Treatment
Scott Weiss, *Brigham and Women's Hospital/Harvard Medical School*

Pharmacogenetics of Membrane Transporters
Kathleen Giacomini, *University of California, San Francisco*

Pharmacogenetics of Nicotine Addiction and Treatment
Neal Benowitz, *University of California, San Francisco*
Huijun Ring, *SRI International*

Pharmacogenetics of Phase II Drug Metabolizing Enzymes
Richard Weinshilboum, *Mayo Clinic College of Medicine*

Pharmacogenomic Evaluation of Antihypertensive Responses
Julie Johnson, *University of Florida in Gainesville*

Pharmacogenomics and Risk of Cardiovascular Disease
Ronald Krauss, *University of California, Berkeley/Lawrence Berkeley National Laboratory*

Pharmacogenomics of Anti-Platelet Intervention Study
Alan Shuldiner, *University of Maryland School of Medicine*

Pharmacogenomics of Arrhythmia Therapy
Dan Roden, *Vanderbilt University*

DOLLARS AND DATES

- **NIGMS and other NIH components together awarded $140 million to establish the network and to fund the first phase, from April 2000 to August 2005.**
- **NIH anticipates spending a total of $152.5 million for the second 5-year phase, which began in September 2005.**